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**A meta-analysis of functional magnetic resonance imaging  
studies of disruptive behavior disorder**

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**Title: A meta-analysis of functional magnetic resonance imaging studies of disruptive behavior disorders**

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Analucia A. Alegria<sup>a</sup>, M.Sc.

Joaquim Radua<sup>b,c</sup>, Ph.D.

Katya Rubia<sup>a</sup>, Ph.D.

<sup>a</sup> Department of Child and Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, United Kingdom

<sup>b</sup> Fundació per a la investigació i la Docència Maria Angustias Gimenez Research Unit, Germanes Hospitalaries and Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain

<sup>c</sup> Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

**Corresponding author:**

Katya Rubia, PhD

Affiliation: Department of Child & Adolescent Psychiatry, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK

Address: De Crespigny Park, London, SE5 8AF, UK.

E-mail: [katya.rubia@kcl.ac.uk](mailto:katya.rubia@kcl.ac.uk)

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**ABSTRACT** (300 words)

**Objective:** Functional magnetic resonance imaging (fMRI) studies in conduct and oppositional defiant disorder have shown inconsistencies. The aim of this meta-analysis of fMRI studies in disruptive behavior disorders was to establish the most consistent brain dysfunctions and to address task and subtype related heterogeneity.

**Method:** Web-based publication databases were searched to conduct a meta-analysis of all whole-brain fMRI studies of youth with disruptive behaviour disorder or conduct problems up to August 2015. Sub-meta-analyses were conducted in functional subdomains of emotion processing, cool and hot executive functions, referring to goal-directed higher cognitive functions without and with motivational and affective significance, and in a subgroup of youth with additional psychopathic traits. Voxel-based group differences in functional activation were meta-analyzed using the Anisotropic effect-size version of Seed-based d Mapping.

**Results:** Across 24 studies, 338 disruptive behaviour disorder/conduct problems youth relative to 298 typically developing youth had most consistent underactivation in rostral and dorsal anterior cingulate and medial prefrontal cortex and ventral caudate. Sub-meta-analyses showed that the medial fronto-cingulate dysfunction was driven by the hot executive function fMRI studies. The sub-meta-analysis of emotion processing fMRI studies showed most consistent underactivation in dorsolateral prefrontal cortex and temporal pole, while cool executive functions were associated with temporal abnormalities. Disruptive behaviour disorder youth with psychopathic traits showed reduced ventromedial prefrontal-hypothalamic-limbic activation, but hyperactivation in cognitive control mediating dorsolateral prefrontal-dorsal striatal regions.

**Conclusion:** The findings show that the most consistent dysfunction in youth with disruptive behaviour disorder is in rostro-dorsomedial fronto-cingulate and ventral striatal regions that mediate reward-based decision making, which is typically compromised in the disorder. Psychopathic traits, on the other hand, have ventromedial prefrontal cortex-limbic dysfunction together with dorsal fronto-striatal

hyperfunctioning, presumably reflecting poor affect reactivity and empathy in the presence of hyperactive executive control. The meta-analysis findings provide potential targets for neurotherapeutic and pharmacological interventions.

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## INTRODUCTION

Disruptive behavior disorder comprises Conduct disorder, defined as frequent violation of the rights of others and age-appropriate social rules, and oppositional defiant disorder, characterized by low frustration tolerance and persistently hostile and defiant behavior (1). It is one of the most prevalent child psychiatric disorders and associated with substantial societal economic burden and increased risk of antisocial personality disorder in adulthood (2).

Youth with disruptive behavior disorder have consistent deficits in emotion processing (3) and executive functions, in particular in response inhibition and attention allocation (4-6).

Executive functions refer to higher cognitive control of thought, action, and emotions (7). A further distinction has been made between “hot” executive functions, which refer to motivationally and emotionally significant tasks and “cool” executive functions that refer to more abstract tasks (7). Youth with disruptive behaviours are most prominently impaired in “hot” executive functions such as in punishment/reward related decision making, measured in tasks of temporal discounting, gambling, reward-reversal and others, suggesting that motivation control is key to the disorder (5,8,9).

Structural magnetic resonance imaging (MRI) studies have found abnormalities in youth with disruptive behaviour disorder relative to controls in ventral and dorsal medial prefrontal cortex, anterior cingulate, and temporo-limbic regions (10-16).

Functional MRI (fMRI) studies have examined most prominently hot and cool executive functions and emotion processing. fMRI studies of hot executive functions found underactivation in disruptive disorder youth compared to controls in predominantly paralimbic regions, including orbitofrontal cortex, ventromedial prefrontal cortex, anterior cingulate (17,18), dorsolateral prefrontal cortex(19), parahippocampal gyrus, caudate, thalamus, temporal(19-21) and inferior parietal cortices(20) (Table 1a, S1a). Few fMRI studies have tested cool executive functions, showing underactivation in dorsolateral prefrontal (24), temporo-parietal (17,22,23), dorsal anterior cingulate, and limbic regions (17) (Table 1b, S1b).

Studies investigating emotion processing showed reduced activation relative to controls in regions of the affect-controlling paralimbic system, including anterior cingulate(25,26), orbitofrontal, ventromedial and dorsolateral prefrontal cortices, temporal lobe, amygdala (25,27-30) and insula (31); some studies, however, found enhanced activation in amygdala (32) and anterior cingulate/orbitofrontal cortex(33) (Table 1c, S1c).

Given the disorder heterogeneity, some studies have attempted to disaggregate brain abnormalities associated with disruptive behaviour disorder alone from those linked to the DSM-5 “limited prosocial emotions” specifier, characterized by psychopathic traits of callousness, remorselessness, lack of empathy, and shallow affect (34), or with the commonly associated ADHD comorbidity. Severity of psychopathic traits in disruptive behaviour disorder has been associated with decreased activation during pain processing and affective and hot executive functions in dorsal anterior cingulate, ventromedial prefrontal and striato-limbic regions(21,29,35-41), while ADHD symptoms were associated with increased insula(31) and decreased frontal activation during emotion processing(42). Direct comparisons showed that non-comorbid conduct disorder relative to ADHD youth had disorder-specific underactivation in ventromedial orbitofrontal cortex during hot executive functions (17), and in limbic areas of anterior cingulate, insula and hippocampus during “cool” executive functions, while ADHD youth had disorder-specific underactivation in inferior prefrontal/dorsolateral prefrontal cortices (5,17,22,23). Although the majority of studies in disruptive behaviour disorder point towards under-recruitment of paralimbic regions that mediate motivation and affect control such as ventromedial prefrontal, anterior cingulate, striatal, and temporo-limbic areas, inconsistencies in findings are likely due to small sample sizes, heterogeneity and comorbidity (e.g., gender, ADHD, psychopathic traits) and/or differences in analytical methodology (e.g. whole brain or region of interest analyses) and/or cognitive domains tested.

The aim of this meta-analysis was to establish the most consistent brain function abnormalities of disruptive behaviour disorder using all published whole-brain fMRI studies - which do not bias findings to apriori hypothesized regions (43). To reduce heterogeneity, sub-meta-analyses were conducted of functional subdomains of emotion processing and hot and cool



executive functions as well as of patients with psychopathic traits. Further, meta-regression analyses assessed effects of gender, medication and ADHD comorbidity. Based on whole-brain fMRI findings (Table 1, S1), we hypothesized that disruptive behaviour disorder youth relative to controls would show most consistent underactivation in paralimbic regions of motivation and affect control such as medial prefrontal cortex, anterior cingulate and temporo-striato-limbic areas. Furthermore, we hypothesized that those with psychopathic traits would show more prominent deficits in striato-limbic regions (16,21,29,35-39), while ADHD comorbidity would be associated with inferior prefrontal dysfunction (5).

## METHOD

### Study selection

A literature search was conducted of whole-brain fMRI studies in children with disruptive behaviour disorder or conduct problems up to August 2015 using PubMed, ScienceDirect, Google Scholar, Web of Knowledge and Scopus databases and a combination of keywords: “Conduct disorder”, “Oppositional defiant disorder”, “conduct problems”, “callous-unemotional”, “psychopathic traits”, “psychopathy”, “disruptive behaviour”, “aggression”, “antisocial behaviour”, plus “fMRI” and “neuroimaging”. Paper references were examined to identify additional studies and additional details from authors were obtained wherever necessary. High quality criteria for study inclusion were: whole brain analyses, matching for age/gender, inclusion of more than 10 subjects, use of standardised categorical or dimensional measures to assess disruptive behaviour disorder/conduct problems, definition of inclusion/exclusion criteria and report of software and statistical tests. Studies were excluded on the basis of: 1) region-of-interest analysis only 2) no statistical case-control comparison 3) no report of peak coordinates and 4) different significance/extent thresholds. MOOSE guidelines for meta-analysis of observational studies were followed (44). To avoid duplication, conjunctive group differences across tasks/task conditions, or main group effects across task conditions were excluded. Peak coordinate and effect-size of significant activation differences between cases and controls were extracted from each contrast of interest for each study.

### Comparison of brain activation

Regional differences in activation during fMRI tasks were analyzed using the anisotropic effect-size version of Seed-based d Mapping software (<http://www.sdmproject.com>), a voxel-based meta-analytic approach (45-47). First, the software recreates the study maps of the effect size of differences in BOLD response between patients and controls converting the  $t$ -value of each peak to Hedges effect size and then applying an anisotropic non-normalized Gaussian kernel so that voxels more correlated with the peak have higher effect sizes.

The software was modified to allow inclusion of a single, combined map with reduced variance for studies sharing subjects (see supplement). This resulted, for example, in a single map for all 7 datasets published by Rubia(17, 22-24). Maps were combined with a standard random effects model, taking into account sample size, intra-study variability and between-study heterogeneity (48). Statistical significance was determined using standard permutation tests and default thresholds (48-51).

Additional sub-meta-analyses were conducted on the cognitive sub-domains: 1) hot executive functions, 2) cool executive functions and 3) emotion processing. Insufficient fMRI studies were available for a sub-meta-analysis on pain empathic processing. Furthermore, a sub-meta-analysis was conducted on fMRI studies of disruptive behavior disorder with psychopathic traits. To examine effects of gender, age, medication and ADHD comorbidity, meta-regression analyses were conducted. Jackknife sensitivity analyses, consisting in repeating the same analysis excluding one dataset at a time, were conducted on all main and subgroup meta-analyses to establish replicability of findings. Last, funnel plots were conducted to detect abnormalities such as studies reporting opposite results or publication bias.

## RESULTS

### Included studies and characteristics

Fifty-three high-quality functional task contrasts from 16 independent samples from 24 fMRI studies were included in the main meta-analysis, comprising 338 youth with disruptive behaviour/conduct problems (mean age: 15.2 years, mean age range: 11.9-17.7 years; 80%

males) and 298 controls (mean age: 15.0 years, mean age range: 11.3-17.9 years; 80% males), taking overlaps into account (Tables 1, S1). Five studies (four testing emotion processing and one pain empathic processing) assessed conduct problems dimensionally without providing a clinical diagnosis (27,28,33,38,52). Across 9 studies there were 108 participants with disruptive behaviour/conduct problems and psychopathic traits and 115 healthy controls. Most (N=11) but not all studies(19,27,28,33,38,52,53) reported ADHD comorbidity rates (0-88%; most over 50%). Twenty-two hot executive function task contrasts were used to create 10 independent brain maps (171 cases; 177 controls), 10 cool executive function task contrasts created 4 independent brain maps (60 cases; 70 controls), and 17 emotion processing contrasts created 8 independent brain maps (169 cases; 130 controls).

### **Main meta-analysis**

The disruptive/conduct problems group compared to controls showed significantly decreased activation in a cluster comprising dorsal and rostral anterior cingulate and medial prefrontal cortex, extending into supplementary motor area and ventral caudate. Cases compared to controls showed no significantly increased activations (Table 2a, Figures 1a, 2a).

### **Cognitive sub-domain meta-analyses**

The subgroup meta-analyses showed that disruptive behaviour/conduct problems youth compared with controls across all hot executive function fMRI datasets had decreased activation in dorsal anterior cingulate/dorso-medial prefrontal cortex extending into supplementary motor area and increased right dorsal caudate activation (Figure 2b, Table 2b); across all cool executive function fMRI datasets they had decreased activation in right superior/middle temporal gyrus, posterior insula and putamen (Figure 2c, Table 2c); and across all emotion processing fMRI datasets they had decreased activation in right dorsolateral prefrontal cortex and left temporal pole (Table 2d; Figure 2d).

**Subgroup meta-analysis in the disruptive/conduct problems group with psychopathic traits**

The subgroup meta-analysis including only disruptive/conduct problems youth with psychopathic traits showed decreased activation relative to controls in a cluster comprising hypothalamus and thalamus extending into ventral striatum and ventromedial prefrontal cortex and increased activation in rostral dorsolateral prefrontal cortex and right dorsal caudate (Table 2e; Figures 1b, 2e).

Findings remained significant when studies using non-diagnosed youth with conduct problems were excluded.

**Meta-regression analyses of effects of age, medication, gender, and ADHD**

The meta-regression analyses showed that 1) increasing age was associated with a progressive hypoactivation in right dorsolateral prefrontal cortex (MNI coordinates:  $x=50$ ,  $y=28$ ,  $z=36$ ; 16 voxels), which overlapped with the reduced cluster during emotion processing; 2) medication was associated with increased activation in bilateral temporal and medial frontal regions, cerebellar vermis, and posterior cingulate/precuneus and with decreased activation in cerebellar vermis, right insula and left hippocampus (see Figure S1), none of which overlapped with any group difference clusters; 3) gender was associated with lower activation, i.e. more severe dysfunction, in left anterior cingulate in the disruptive/conduct problems group relative to controls; 4) ADHD comorbidity across the 11 available studies with this information was not significantly correlated with neural underactivation relative to controls.

**Reliability analyses**

Whole-brain jackknife sensitivity analyses showed that the main meta-analysis finding in dorso-rostral anterior cingulate/medial prefrontal cortex and ventral caudate was robust and replicable (Table 3), as preserved in all but two brain map combinations. For the subgroup meta-analyses, the brain difference findings were preserved in all but one or two combination of brain maps (Supplementary Tables S2-S5).

**Publication bias**

Funnel plots showed that studies with smaller samples were associated with smaller effect sizes, which is opposite to that associated with publication bias.

**DISCUSSION**

The meta-analysis across 53 whole-brain fMRI task contrasts showed that disruptive/conduct problems youth have most consistent deficits in the closely interconnected dorsal and rostral anterior cingulate and medial prefrontal cortex involved in top-down-regulation of motivation and affect and in ventral striatum which is part of the same affect control network. The dorsal and ventral medial prefrontal cortex dysfunction largely arose from the hot executive function sub-domain studies, suggesting it is associated with reward-related decision making.

The dorso-rostral anterior cingulate/medial prefrontal cortex together with their close connections to the ventral striatum and limbic regions lie at the interface between emotion and cognition and form part of the mesolimbic fronto-striatal dopamine pathway modulating reward processing (54), reward-based decision making and motivation control (55). Recent meta-analyses and fMRI reviews of decision making show that both structures are crucial for the integration of affective and reward information into cognitive processes governing decision making (56,57), such as reappraisal (57,58), reward-based decision making (55,59,60), reward processing (61), reinforcement learning (62,63), and inter-temporal choice (55,56,64). The dysfunction finding is parallel to 2 recent whole-brain structural MRI meta-analysis findings of reduced grey matter in youth with conduct problems and in antisocial behaviour in anterior cingulate and dorsomedial and frontopolar prefrontal cortices, respectively (16,65). This abnormality in dorsomedial prefrontal mediated decision making and ventral caudate reward processing regions may be the neural underpinning for evidence that perturbed reward-based decision making is key to conduct disorder with and without psychopathy and more common than perturbed empathy or threat sensitivity (66). It may contribute to the maladaptive impulsive-aggressive, norm-violating behaviors observed in this population (6), possibly due to increased frustration resulting from poor decisions, leading to reactive aggression (67). Male

gender was associated with more severely decreased dorsal anterior cingulate function. However, this must be interpreted with caution as most studies included over 50% males. A caveat is that the majority of fMRI studies included in this meta-analysis tested hot executive functions, given consistent neurocognitive impairments (5,6,9,66), which has likely biased the findings. Future meta-analyses of a larger number of fMRI studies of emotion processing may reveal more orbitofrontal-limbic abnormalities.

The cool executive function sub-meta-analysis revealed right superior/middle temporal dysfunction in the disruptive/conduct problems group. The temporal lobes have been suggested to be dysfunctional in neurobiological theories of conduct disorder/psychopathy(13, 68), because they are among the most consistently observed structural deficit regions (10,15,16,65,69). The temporal lobes form part of the paralimbic motivation system and together with the amygdala mediate stimulus-reinforcement learning (70); the temporal lobe hypo-activity may hence reflect insufficient motivation (5). Alternatively, superior temporal regions have also been associated with attention functions (71,72) which are affected in the disorder (4, 5).

The decreased right dorsolateral prefrontal activation during emotion processing also suggests poor frontal top-down cognitive control over emotion processing, a key functional role of this region (58,73), while reduced left temporal pole function may reflect impaired socio-emotional processes(74). Interestingly, older patients had more dorsolateral prefrontal dysfunction, which may suggest progressive age-related impairments. However, the reliability analysis showed that the temporal dysfunction was due to only two fMRI studies (31, 21) while dorsolateral prefrontal dysfunction was due to the largest study only (31). Unexpectedly, we did not observe abnormalities in limbic regions such as amygdala during emotion processing. The amygdala is a relatively small region and hence rarely observed in whole brain (only in 2 studies (37,41)), but mostly in region of interest fMRI studies (25,28-30,33). Furthermore, during negative emotions, amygdala activation has been found to be decreased in conduct disorder with psychopathic traits, but increased in those without (67), which may have resulted in negative findings as most included studies did not screen out individuals with psychopathic traits.

The sub-group meta-analysis findings in youth with disruptive/conduct problems and psychopathic traits differed from those in the whole group, in line with evidence for different neurological etiological mechanisms in conduct disorder with and without psychopathic traits (52,66,67,75). Thus, the functional deficits in this subgroup were in ventromedial prefrontal- limbic regions known to be involved in reward and decision making and in areas of affective reactivity, especially to negative emotions, such as hypothalamus and thalamus(76,77). Hypothalamus hypoactivity is consistent with evidence for reduced hypothalamic-pituitary-adrenal neuroendocrine system and cortisol levels in this group (79,80), that furthermore correlated with psychopathic traits (80, 81). The underfunctioning in ventromedial prefrontal-hypothalamic regions, both closely interconnected with the amygdala, may play a role in the psychopathy symptoms of reduced affect such as reduced responsiveness to threat and distress cues, lack of empathy, guilt and low anxiety levels (66,67,82,83). The ventral striatum is a key region of reward and loss processing, thought to be at the core of psychopathic traits (84-86). The deficit findings are in line of Blair's psychopathy model (66,67) of ventromedial prefrontal, amygdala, hypothalamus and striatal abnormalities, with the exception that we found no amygdala underactivation. As discussed above, this may be due to the use of whole-brain fMRI analyses and a prevalence of fMRI studies of reward-based decision making. The rostral dorsolateral prefrontal cortex and dorsal caudate overactivation in the disruptive/conduct problems group with psychopathic traits is in line with findings of abnormally increased caudate volumes in psychopathic adults and violent offenders (87,88), and higher structural connectivity in cingulo-fronto-striatal tracts in adolescent arrestees that correlated with grandiose-manipulative traits (89), and of correlations between dorsolateral prefrontal hyperactivity and psychopathic traits (90). Rostral dorsolateral prefrontal cortex and caudate are involved in planning (91, 92) and enhanced activity in these regions is in line with neurocognitive studies showing no deficits or even superior executive functions such as planning, set-shifting and language abilities (93-96) and matches the defining features of proactive, planned and goal-directed aggression (as opposed to frustration/threat-induced reactive aggression in those without psychopathic traits) (97) as well as with their ability to manipulate, cheat and con. A

dysfunctional affect and a hyperfunctional executive control system in disruptive groups with psychopathic traits provides neurofunctional support for behavioural theories of good executive functions in the presence of dampened affect. Thus, it has been suggested that a hypoactive bottom-up affective system (reflecting reduced affective reactivity and lower anxiety), together with good top-down executive control over emotions may lead to less emotional interference with cognitive functions, explaining superior performance in psychopathy (93-96).

The subgroup meta-analysis on disruptive/conduct problems with psychopathic traits, however, should be treated with caution as studies were heterogeneous in methods, informants and cut-off scores for psychopathic traits. Future studies need to clearly distinguish disruptive behaviour disorder groups with and without psychopathic traits based on internationally agreed age-normed standardized measures from multiple informants to establish the neurofunctional underpinnings of both subtypes (98-100).

The meta-regression analyses showed that ADHD comorbidity, age or medication had no impact on dysfunctions, suggesting they are specific to disruptive behavior disorder. Despite evidence of dorsal anterior cingulate underfunctioning in ADHD during executive functions (5, 46), comparison between ADHD-comorbid and non-comorbid conduct disorder showed that dorsal anterior cingulate underactivation was specific to conduct disorder(5,17); also, rostro-dorsal anterior cingulate dysfunction in conduct disorder in fMRI studies of emotion processing remained when ADHD was controlled for (25) and correlated specifically with conduct disorder symptoms and aggressive behavior (25,37,101). Structural analyses also found anterior cingulate volume to be associated with disruptive behaviour disorder when ADHD was covaried for (102). Hence, rostro-dorsal anterior cingulate underactivation findings in ADHD may be associated with commonly co-occurring antisocial features(5). Meta-analytic fMRI evidence in ADHD also suggests more prominently lateral rather than medial frontal underactivation during executive functions (45,46). Alternatively, reward-based decision making, which is also impaired in ADHD (5), even if more accounted for by antisocial behaviours in dimensional analyses (9), may be a transdiagnostic endophenotype of both disorders, with a common underlying neural substrate in dorsomedial prefrontal cortex. Ventral striatum underactivation is also a consistent



meta-analytic finding in ADHD during reward anticipation(103), however based on region of interest studies. This dysfunction has not been observed in whole-brain meta-analyses of ADHD, which could explain the lack of association with ADHD comorbidity. Alternatively, ventral striatum dysfunction in ADHD may be associated with comorbidity with conduct disorder which is rarely excluded in ADHD fMRI studies.

This study has a number of limitations inherent to all meta-analyses. First, peak and effect size based meta-analyses use data from published studies rather than raw statistical brain maps, increasing the likelihood of less accurate results (48). Second, different studies used different statistical thresholds. Third, while the voxel-wise meta-analytic method provided good control of false positive results, false-negative results are more difficult to avoid, making results more conservative (48). Fourth, although substance abuse is common among disruptive/conduct problems youth and has an important effect on brain structure and function (104,105), many studies including youth with substance use disorder comorbidity did not report case numbers (18,21,28,33,38,52,101), hampering our ability to examine its effect. It is also likely that patients with pure oppositional defiant disorder differ in their neurofunctional substrates from those with pure conduct disorder and future studies should address this heterogeneity. Fifth, studies have suggested differences between early and late-onset disruptive behaviour disorders(11,31), but there was not sufficient information to conduct subtype meta-analyses. Sixth, mean age only ranged from 11.9 to 17.4 years, and the meta-regression analysis with age should therefore be taken with caution. Seventh, Seed-based d Mapping software does not directly take into account the reported cluster size, which could improve the recreation of effect size maps. However, cluster size is indirectly taken into account of through use of cluster local peaks, and the fact that cluster size depends on the peaks' height and the local covariance between neighboring voxels. Last, the "cool executive function" sub-meta-analysis was relatively underpowered with only 8 datasets, and 50% of studies were from the same lab, using the same 13-14 subjects, which makes the meta-analysis findings not representative. Further research on cool executive functions in disruptive behaviour disorder/conduct problems groups is still merited.

In summary, this is the first meta-analysis of fMRI deficits in disruptive behaviour/conduct problems youth. It shows that the core dysfunction is in rostro-dorsal medial fronto-cingulate regions that exert top-down control over interconnected limbic motivation systems such as the also underactivated ventral caudate and underlie reward-based decision making, which is typically compromised in the disorder. Psychopathic traits within the disorder are more prominently associated with ventromedial frontal-hypothalamic-limbic underfunction together with dorsolateral prefrontal-striatal hyperfunctioning, presumably reflecting poor empathy and affect reactivity together with and perhaps caused by enhanced dorsolateral prefrontal-striatal top-down control. Finding dissociated neuro-functional correlates in the disruptive behavior groups with and without psychopathic traits adds to increasing evidence for different underlying neurobiology and support the utility of the DSM-5 callous-unemotional specifier in the classification of conduct disorder youth. The meta-analysis findings provide potential targets for neurotherapeutic and pharmacological interventions.

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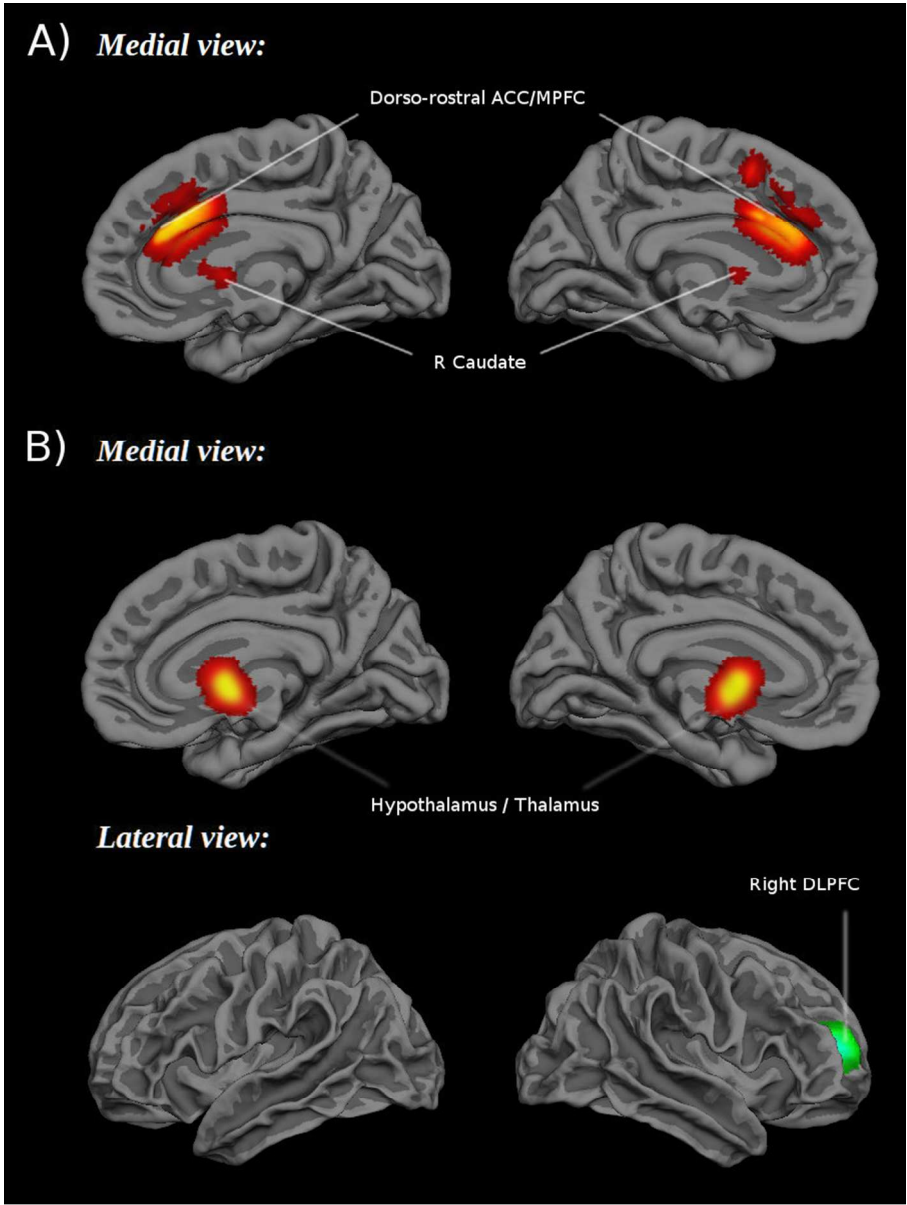
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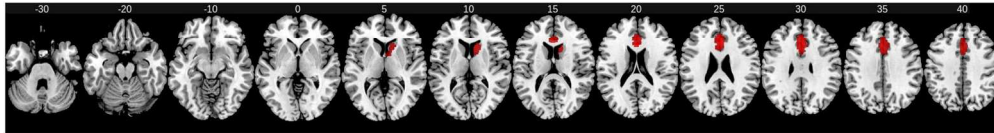
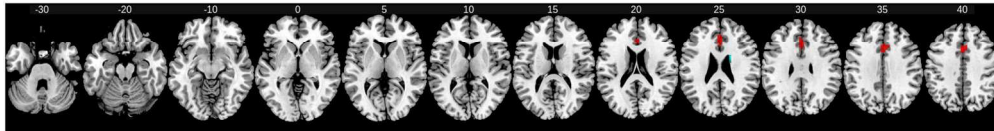
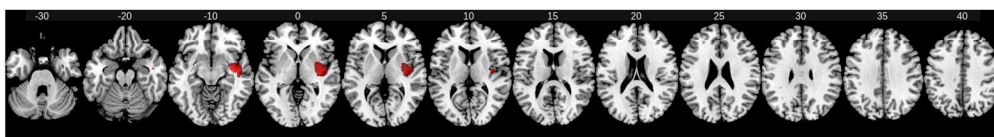
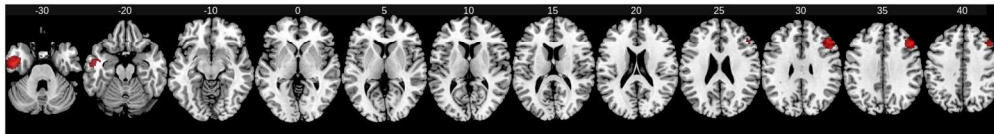
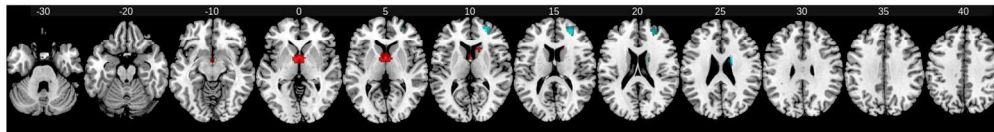
**FIGURE LEGENDS**

**FIGURE 1:** Results of the main meta-analysis and of the subgroup meta-analysis of disruptive behaviour disorder/severe conduct problems plus psychopathic traits. **A)** Decreased activation in disruptive behaviour disorder/conduct problem youth compared to healthy controls is shown in red in the dorsal and rostral anterior cingulate cortex /dorsal and rostral medial prefrontal cortex /supplementary motor area and the ventral caudate. **B)** Decreased activation in youth with disruptive behaviour disorder/conduct problem plus psychopathic traits compared to healthy controls is shown in red in the hypothalamus/thalamus extending into ventral medial prefrontal cortex and ventral striatum. Increased activation is shown in green in the dorsolateral prefrontal cortex. Note that the increased dorsal caudate activation finding is not shown in Figure 1 but in Figure 2.

**FIGURE 2:** Axial sections showing regions that were significantly reduced (red) and increased (green) in disruptive behavior disorder/conduct problem youth relative to healthy controls. **A)** Main meta-analysis including all tasks. **B)** Subdomain meta-analysis on hot executive function tasks. **C)** Subdomain meta-analysis on cool executive function tasks. **D)** Subdomain meta-analysis on emotion processing tasks. **E)** Subgroup meta-analysis on disruptive behavior disorder/conduct problem youth plus psychopathic traits compared to healthy controls. MNI z co-ordinates are indicated for slice distance (in mm) from the intercommissural line. The right side of the image corresponds to the right side of the brain.



317x423mm (72 x 72 DPI)

**A) Main meta-analysis on DBD/CP compared to healthy controls including all tasks****B) Subdomain meta-analysis on hot executive function tasks****C) Subdomain meta-analysis on cool executive function tasks****D) Subdomain meta-analysis on emotion processing tasks****D) Subgroup meta-analysis on DBD/CP+PT compared to healthy controls**

141x139mm (300 x 300 DPI)





TABLE 1. Summary of whole-brain fMRI studies of DBD/CP included in the main meta-analyses						
Paper	DBD/CP group		HC group		Reduced activation (relative to HC)	Enhanced activation
	N	Males (%)	N	Males (%)		
1a) Studies using hot EF tasks						
Rubia (17)	14	100	16	100	R OFC/vMOFC	-
Crowley (19)	20	100	20	100	B r/vMPFC, L OFc, B r/dACC, B insula, B precentral, L postcentral g, R pre-SMA, L claustrum, R caudate/putamen, R amygdala, R MTG/STG, L hippocampus, L precuneus, L PCC, R IPL, R lingual g, L & R Cb, B rACC, B STG/R MTG/ITG, R precuneus, R fusiform g, B Cb	B dMPFC, L OFC, B MTG;L ITG, L brainstem/ pons, L culmen, R paracentral g., R PCC , B MTG, L prec.
Kalnin (53) <sup>e</sup>	22	59	22	59	-	-
Cohn (40) <sup>g</sup>	22 <sup>a</sup>	73	236	87	-	-
White (20) <sup>e</sup>	15	73.3	15	66.7	L MPFC, L SFG, L DLPFC, R IFG/precentral g, R MPFC, R MTG, L Middle Occipital g	-
Marsh ( 41) <sup>b</sup>	14	57	14	79	amygdala	-
Finger (21) <sup>b</sup>	14	64	14	64	-	B MFC, R caudate
Finger (18) <sup>b</sup>	15	60	15	60	R OFC, L MFC, L SFC, B IFG, L IPL, B MTG, L caudate, L Cb, OFC, L DLPFC, R parahippocampal g	-
White et al. (42) <sup>b</sup>	17	76.5	19	47	B SPL, B IPL, L cuneus	-
White et al. (42) <sup>b</sup>	17	76.5	19	47	-	-
White et al. (36) <sup>b</sup>	15	80	17	52.9	L MTG	-
1b) Studies using Cool EF tasks						
Rubia et al. (22)	13	100	20	100	R PCC/precuneus, L IPL, R postcentral/STG/IPL	-
Rubia et al. (17)	14	100	16	100	R insula/hippoc./premotor, L dACC, B Cb/TL/ thalamus/occipital/ hippocampus/ L PCC/precuneus	-
Rubia et al. (24)	13	100	20	100	R STG/MTG, R precuneus, R DLPFC	-
Rubia (23)	14	100	20	100	R IPL/ precentral g, L STL/IPL, L precuneus, cuneus	-
Marsh et al. (41) <sup>b</sup>	14	57	14	79	-	-
White et al. (42) <sup>b</sup>	17	76.5	19	47	-	-
White et al. (42) <sup>b</sup>	17	76.5	19	47	R MTG, R thalamus	-
White et al. (36) <sup>b</sup>	15	80	17	52.9	-	-
1c) Studies using emotion processing tasks						
Herpertz et al. (32)	22	100	22	100	-	-
Passamonti et al. (31) <sup>e</sup>	40	100	20	100	R DLPFC, L MTG, L ant insula	-
Fairchild et al. (30)	20	0	20	0	-	-
Sebastian et al. (33)	17	100	17	100	-	rACC/OFC
Sebastian et al. (52)	31	100	16	100	-	-

Cohn et al. (39)	25 <sup>c</sup>	72	26	89	-	-
O'Nions et al. (27) <sup>b</sup>	16	100	16	100	R r/vMPFC	-
Marsh et al. (29) <sup>b,e</sup>	12	58.3	12	50	R STG	-
Marsh et al. (41) <sup>b</sup>	14	57	14	79	R STG, R PCC, Precuneus	-
Jones et al. (28) <sup>b</sup>	17	100	13	100	-	-
White et al. (42) <sup>b</sup>	17	76	19	47	-	L SFC, R MFC
<b>1d) Studies using empathic pain tasks</b>						
Lockwood et al. (38)	37	100	18	100	L STG/post insula, R Cb, R MTG, R caudate, GP, subst nigra, L thalamus, L SMA, L & R IFC/insula, L DLPFC/IFC, R Cb, R SFC, L ACC, L precuneus	L Parahippocampal g., L Cb
Marsh et al. (37) <sup>b</sup>	14	57	21	71	L SFC, R insula, L amygdala/uncus	-

*Note:* Only whole-brain results are reported for the studies. Also, the results of the studies are summarized in this table only for the benefit of the reader, but the meta-analysis is not based on these labels, but on numerical voxel data.

<sup>a</sup> Nineteen of 20 subjects met DSM-IV CD diagnostic criteria and all met diagnosis of substance use disorder.

<sup>b</sup> Study only included youth showing a high score of PT or callous unemotional traits, hence included in the DBD/CP +PT subgroup meta-analysis.

<sup>c</sup> Sample recruited from a cohort of adolescents who were first arrested by the police before the age of 12 years.

<sup>d</sup> Mean age and SD were reported separately for early onset and late onset conduct disorder respectively.

<sup>e</sup> Results reported here were obtained through a personal communication with the author or the supplement.

<sup>f</sup> Only age range was reported.

<sup>g</sup> note results reported in the paper were not statistically significant at the whole-brain level and thus excluded from the meta-analysis.

ACC= anterior cingulate cortex; ant= anterior; B= bilateral; Cb= cerebellum; CP= severe conduct problem; dACC= dorsal anterior cingulate cortex; DBD= disruptive behavior disorder; DLPFC= dorsolateral prefrontal cortex; dMPFC= dorsomedial prefrontal cortex; EF= Executive functions; Ext= extending; g= gyrus; GP= globus pallidus; HC= Healthy controls; IFG= Inferior frontal gyrus; IPL= inferior parietal lobe; ITG= inferior temporal gyrus; L= left; MFC= middle frontal cortex; MTG= middle temporal gyrus; OFC= orbitofrontal cortex; PCC= posterior cingulate cortex; Post= posterior; Prec= precuneus; R= right; rACC= rostral anterior cingulate cortex; rMPFC= rostral medial prefrontal cortex; SFC= superior frontal cortex; SMA= supplementary motor area; Sup= superior; STG= superior temporal gyrus; SPL= superior parietal lobe; TL= temporal lobe

**TABLE 2. Results of the meta-analysis of whole-brain fMRI studies in youth with DBD/CP compared with healthy controls including all tasks, by cognitive sub-domain and presence of PT.**

Contrast	MNI coordinates (x, y, z)	Effect size	95% CI <sup>a</sup>	SDM Z Score	P value	No. of voxels	Cluster breakdown (No. of voxels)
<b>a) Main meta-analysis for all tasks</b>							
DBD/CP < HC							
Rostro-dorsal ACC/MPFC/ SMA	0, 20, 24	-0.08	-0.12,-0.04	-1.345	< 0.00005	1445	dACC: BA24/BA32 (850), rACC: BA24/BA32 (52), dMPFC: BA8/BA9 (100), rMPFC: BA9/10 (33), SMA: BA6 (12)
Ventral caudate	14, 18, 12	-0.07	-0.11,-0.03	-1.087	<0.0005	307	R caudate head ventral (152)
<b>b) Hot executive functions</b>							
DBD/CP < HC							
dACC/dMPFC/ SMA	0, 12, 38	-0.09	-0.16,-0.03	-1.034	< 0.005	335	dACC: BA24/32 (264), dMPFC BA9/32 (58), SMA: BA6 (13)
DBD/CP > HC							
Dorsal striatum (caudate)	18, 0, 26	0.11	0.06-0.16	1.075	< 0.00005	32	R caudate body dorsal (32)
<b>c) Cool executive functions</b>							
DBD/CP < HC							
Right superior/middle temporal /insula/putamen	40, -12, -8	-0.16	-0.24,-0.16	-1.133	<0.00005	1131	R STG: BA22 (363), R MTG: BA21 (75), R putamen (331), insula (330)
<b>d) Emotion processing</b>							
DBD/CP < HC							
Left middle/inferior temporal/ fusiform	-48, -8, -26	-0.10	-0.15,-0.05	-1.126	< 0.00005	637	L ITG: BA20/BA21 (464), L MTG: BA20/BA21 (167), FG (6)
Right middle frontal	48, 26, 34	-0.11	-0.17,-0.06	-1.222	< 0.00005	522	R DLPFC: BA9 (502), BA46 (20)
<b>e) DBD/CP+PT subgroup meta-analysis for all tasks</b>							
DBD/CP+PT < HC							
Hypothalamus/thalamus/ vMPFC/ventral striatum	0, 0, 0	-0.11	-0.16,-0.05	-1.027	< 0.00005	555	Hypothalamus (244), thalamus (150), VS (50), vMPFC: BA 25 (40)
DBD/CP+PT > HC							
Rostral Dorsolateral PFC	24, 48, 12	0.15	0.09,0.21	1.189	<0.000001	276	Rostral DLPFC (260)
Right striatum (caudate)	18, 0, 26	0.17	0.10,0.24	1.182	<0.000001	4649	R caudate body (46)

BA= Brodmann area; dACC= dorsal anterior cingulate cortex; DBD/CP= disruptive behaviour disorder /severe conduct problems; DLPFC: dorsolateral prefrontal cortex; dMPFC= dorsomedial prefrontal cortex; HC= healthy controls; ITG= inferior temporal gyrus; L= left; MTG= medial temporal gyrus; PT= psychopathic traits/callous unemotional traits; R= right; RL= rostralateral; rACC= rostral anterior cingulate cortex; rMPFC = rostral medial prefrontal cortex; SDM= Seed-

based d Mapping; SMA= supplementary motor area; STG= superior temporal gyrus; vMPFC= ventromedial prefrontal cortex; VS= ventral striatum

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**TABLE 3. Results of the jackknife reliability analyses of the main meta-analysis findings based on 52 different task contrast results from 16 independent samples.**

	Study	Contrast included in brain maps	r/d ACC/ PFC/SMA (0, 20, 24) <sup>a</sup>	R Caudate (14, 18, 12)
1	Herpertz et al. (32)	Negative/positive > neutral valence images	Yes	Yes
2	Passamonti et al. (31)	Angry/sad > neutral expression	Yes	Yes
3	Fairchild et al. (30)	Angry/sad > neutral expression	Yes	Yes
4	Marsh et al. (29) Marsh et al. (41) Marsh et al. (37)	Fearful/angry > neutral expression Positive > negative valenced objects; categorizing illegal > legal words; Incongruent > congruent trials One's > Other's pain; Other's > One's pain	Yes	Yes
5	Jones et al. (28)	Fearful > neutral expression	Yes	Yes
6	White et al. (42)	Eye gaze task: Neutral > anger expression; Fear > neutral expression; Fear congruent > fear incongruent; Incongruent > congruent (interference effect)	Yes	Yes
7	Sebastian et al. (33) Sebastian et al. (52) O'Nions et al. (27)	Fearful eyes: (fear/eyes > calm/eyes) > (fear/face > calm/face) Affective ToM > cognitive ToM/physical causation Tom > physical causation	Yes	Yes
8	Cohn et al. (39) Cohn et al. (40)	Fear Conditioning: Conditioned > unconditioned MID task: Reward > neutral trial anticipation; Loss > neutral trial anticipation; Reward hit > reward miss; Loss miss > loss hit	Yes	Yes
9	Lockwood et al. (38)	Pain > no pain	No	No
10	Rubia et al. (17) Rubia et al. (22) Rubia et al. (23) Rubia et al. (24)	Rewarded CPT: Rewarded > non-rewarded targets; Non-rewarded target > non-targets. Stop task: Failed Stop > Go; successful stop > failed stop. Switching task: Switch trials > repeat trials Simon task: Incongruent > oddball trials; oddball > congruent trial.	Yes	Yes
11	Crowley et al. (19)	Colorado balloon game: risky decision making > instructions; Winnings>no outcome; Losing > no outcome	No	No
12	Kalnin et al. (52)	Emotional Stroop: Violent > nonviolent words	Yes	Yes
13	White et al. (20)	Choose not open > Choose to open appetitive door; Appetitive choice > physical threat choice; Appetitive choice > contamination choice; Physical threat > appetitive stimuli feedback; Appetitive stimuli > contamination threat feedback	Yes	Yes
14	Finger et al. (21)	Reversal learning: Punished reversal errors > rewarded correct responses	Yes	Yes
15	Finger et al. (18)	Passive avoidance task: Early > non early trials; Rewarded correct hits > punished commission errors; Punished commission errors > rewarded correct hits	Yes	No
16	White et al. (36)	Emotion-attention bars task: Fear > neutral expressions; High > low attentional load	Yes	Yes
<b>Total</b>			<b>14/16</b>	<b>13/16</b>

<sup>a</sup> Yes= Brain region remains significantly decreased in the jackknife analysis when the independent sample in question is excluded from the meta-analysis; No= Brain region is no longer significantly decreased when the independent sample in question is excluded.

ACC= anterior cingulate cortex; D=dorsal; R= rostral; MID= Monetary incentive delay; MPFC= medial prefrontal cortex; SMA= supplementary motor area; ToM= theory of mind.

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